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Letter to the Editor

Endothelin receptor blockade and nitric oxide bioactivity [Cardiovascular Research 2001;49:146–151]☆

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In a recent paper, Verma et al. reported abnormal endothelium-dependent relaxation to acetylcholine in isolated internal mammary arteries obtained from patients with coronary artery disease [1]. The authors also observed a moderate increase of the maximum response but not of the sensitivity of these relaxations after 20 min of incubation with micromolar concentrations of either bosentan, a non-selective ET receptor antagonist, BQ-123 (an ET_A selective compound) or BQ-788 (an ET_B selective compound at low concentrations). The improvement of endothelium-dependent relaxation averaged between 10 and 17% of complete relaxation compared to control experiments, and was not present in endothelium-denuded vessels and not evident in response to the endothelium-independent vasodilator sodium nitroprusside according to the authors' unpublished data. The authors concluded that both ET_A and ET_B receptors contribute to 'endothelial dysfunction' and that blocking both the ET_A and the ET_B receptor may have endothelial protective effects in human internal mammary arteries. However, there are several issues that must be taken into account when interpreting these data.

First, the clinical characteristics and treatments of the study patients, a considerable number of which were women, deserve mentioning. More than half of the patients had a positive family history for coronary artery disease, were smokers, and/or had hypercholesterolemia. It is surprising to learn that despite the elevated plasma lipids and in view of the beneficial effects of statins in the secondary prevention of coronary artery disease, none of the patients was on statin therapy, a treatment that has also been shown to improve endothelium-dependent vasomotion [2,3].

Second, the authors refer to atherosclerosis of the internal mammary artery (IMA). However, even in patients with atherosclerosis in the coronary circulation, atherosclerotic structural changes rarely occur in the IMA [4,5] making it the conduit of choice for coronary bypass surgery. It is known that atherosclerotic changes may develop after this artery has been grafted as a bypass conduit or in cardiac transplant recipients [6]. Therefore, the authors' notion that 'ET-1 is increased in atherosclerotic IMA' is hard to follow.

Third, endothelium-dependent relaxation in this vessel has been extensively studied, and most studies, including our own, have shown that endothelium-dependent relaxation in response to acetylcholine is preserved in the IMA [7–10]. How can the clearly abnormal relaxant response to acetylcholine, reaching relaxation of only 40% of precontraction, observed in the authors' experiments be explained? The authors refer to one previous study on endothelium-dependent relaxation in human IMA, which showed relaxant responses between 0 and 70% despite comparable ecNOS immunostaining in histologic sections in the vessels investigated [11]. Not surprisingly, vessel culture for 24 h with sepiapterin or L-arginine had no effect on the relaxant response which was abnormal to begin with [11]. The aforementioned study and the one by Verma et al. are in strong contrast to several other studies by different laboratories demonstrating preserved endothelium-dependent relaxation in response to acetylcholine in human IMA [7–9,12,13].

As correctly pointed out in the editorial by Hoogerwerf [14], careful intraoperative handling of the arteries is of paramount importance for the functional integrity of the vessels as bypass conduits and probably contributes to long-term graft patency [10,15]. Indeed, our previous

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studies revealed that intraoperative handling of the graft is a crucial determinant of endothelium-dependent responses in the IMA and also in other grafts [8,10]. Using acetylcholine as a stimulus, it has been demonstrated that endothelium-dependent relaxations average between 75 and more than 95% of precontraction in arteries obtained from CAD patients with multiple risk factors [7–9,12,13]. This notion is also supported by a study demonstrating that mechanical manipulation such as distension does indeed impair endothelial-dependent responses to acetylcholine [16].

In their article, the authors repeatedly refer to 'endothelial dysfunction' as simply the 'net balance of endothelium-derived vasoconstriction and vasodilation'. Although attractive, this view does not take into account the complexity of the abnormalities occurring in the injured endothelium [17] determining the endothelial phenotype. Thus, impairment of NO-mediated endothelium-dependent relaxation represents only one aspect of the spectrum of 'endothelial dysfunction' which comprises the dysregulation of all endothelial cell functions, including cytokine release, lipid metabolism, morphological cellular changes, disturbances of coagulation, etc. [17,18]. Abnormal endothelium-dependent vasomotion as part of 'endothelial dysfunction' not only occurs in atherosclerosis, but also in conditions such as heart failure and pulmonary hypertension. Several previous studies have shown that ET receptor blockade can improve or even reverse this abnormality (reviewed in Ref. [19]).

Finally, the authors claim an 'equal contribution of both ET_A and ET_B receptors towards endothelial function in human IMA' based on their observations of responses to acetylcholine in absence or presence of receptor specific ET antagonists. Moreover, demonstrating a 13% increase in endothelium-mediated relaxation after acute ET_B receptor blockade with BQ-788 at a concentration of 1 μmol/l, the authors interpret this finding as: (a) ET_B receptors contributing to impairment of 'NO-mediated' relaxation in human arteries; and (b) that both ET_A and ET_B receptors equally impair this relaxation. The first assumption cannot be the case since NO synthase inhibition only in part blocks the relaxant response to acetylcholine in the human IMA [12,20] and acetylcholine also causes endothelium-dependent hyperpolarization in this vessel [21]. Moreover, it is likely that at the concentration used in vitro, BQ-788 loses its selectivity over the ET_B receptor. Furthermore, Verma et al. postulate that ET_B receptors in the IMA do not mediate relaxation and are not linked to NO bioactivity, referring to a previous publication [22] but without performing the appropriate experiments with an NO-synthase inhibitor. In fact, it has been previously shown that ET_B receptor stimulation may cause relaxation in human IMA [23].

It was suggested in the editorial by Hoogerwerf that more animal studies should be done to implement these finding into clinical use [14]. It has been previously shown that blockade of ET_A receptors improves NO bioactivity and endothelium-dependent NO-mediated relaxation in the thoracic aorta of atherosclerotic apolipoprotein-deficient E mice [24]. Similarly, indices of increased NO bioactivity have been found after ET blockade in coronary effluents of perfused rat hearts, and similar effects were seen with ET_A selective and non-selective ET_A/ET_B receptor antagonists. Interestingly, no effect was observed with selective ET_B receptor blockade alone [25]. In humans ET_A blockade improves NO-mediated vascular function in the brachial artery in vivo which can be blocked by ET_B receptor blockade [26], and in a recent clinical study, improved acetylcholine-mediated vasomotion in coronary arteries of patients with coronary atherosclerosis after treatment with the ET_A receptor antagonist BQ-123 has been demonstrated [27]. Taken together, the results from these studies strongly are consistent with the concept that ET_A and not ET_B receptors are responsible for increases in NO bioactivity after acute or chronic ET receptor blockade.

As endothelin receptor antagonists are reaching the clinical arena, the therapeutic potential of this new class of drugs must be carefully assessed [28]. Combined ET receptor antagonists, including bosentan, have unquestionably provided a great step in the therapy of patients with advanced congestive heart failure. The majority of studies, experimental ones as well as clinical ones, investigating physiopathologies such as heart failure, endothelium-dependent vasomotion, and hypertension, have shown beneficial effects through blockade of the ET_A receptor, in most cases irrespective whether the ET_B receptor was blocked or not. The data presented by Verma et al. essentially support this notion, demonstrating comparable effects between the ET_A selective antagonist BQ-123 and bosentan on endothelium-dependent vasomotion.

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